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Idiopathic splanchnic vein thrombosis: is it really idiopathic?

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Splanchnic vein thrombosis (SVT) occurring in association with a clonal myeloproliferative neoplasm (MPN) is puzzling and difficult to manage for doctors who care about myeloid disorders as well as those who care about thromboembolic diseases. The phenotype of myeloproliferation is frequently that of a latent disease making diagnosis of an SVT-associated MPN challenging. Also the benefit of using cytoreductive agents is unproven, making therapy uncertain.

In this issue of Haematologica, Carrà and colleagues provide a new piece of the puzzle.1 They reported 15 consecutive cases of idiopathic SVT presenting with mutations involving one or more of the 30 myeloid genes of their next generation sequencing (NGS) panel. In 7 cases, the authors found clonal hematopoiesis of uncertain potential (CHIP), i.e. acquired somatic mutations in leukemia-associated driver genes in individuals without underlying hematological malignancies.

Even though the Carrà’s data mirror those recently published by Magaz et al. in 74 patients with idiopathic SVT,2 the reported results have different hints of interest. The first is that the authors, after setting in >2% the variant allele frequency threshold, reported a CHIP prevalence of 46% (95% confidence interval, 21 to 73%) that is the highest even reported. CHIP occurs in about 10% of healthy people after 70 and about 5% before 65 years. This means the CHIP prevalence in the Carrà’s study is nearly 10-fold higher than that expected in the general population of comparable age. This figure is higher than the 37.8% CHIP prevalence of the Magaz study in
idiopathic SVT, and the 25% prevalence in people with solid cancers. These figures, even though obtained by small numbers, support a role of CHIP in idiopathic SVT.

A second concept of clinical interest is that SVT-associated CHIP contrasts with the dominant notion that CHIP is linked to cardiovascular diseases, possibly related to pro-inflammatory interactions between clonal derived leukocytes and vascular endothelial cells. Considerable data indicate risks of coronary heart disease and stroke are higher in persons with CHIP than in those without CHIP. The clinical relevance of these results is certified by the fact that specialized CHIP clinics with multidisciplinary teams of oncologists, haematologist and cardiologists have been recommended.

Recently, a relationship between CHIP and risk of venous thromboembolism (VTE) has been suggested. This suggestion was originated by a study testing whether individuals with JAK2V617F-positive CHIP had a population of clonal neutrophils primed to produce neutrophils extracellular traps implicated in the pathogenesis of vein thrombosis. In a large case-control cohort (10,893 individuals), the authors documented that JAK2V617F mutant CHIP was powerfully associated with major venous thrombotic events. Subsequent studies reported discordant results. In 11695 patients with solid cancers no significant association between any CHIP mutations, including JAK2V617F, and risk of thrombotic events was evidenced. However, a pilot retrospective observational study of 61 subjects with unprovoked pulmonary embolism reported 20% CHIP-associated somatic mutations.

The study of Carrà et al., and of Magaz et al., bring evidence that CHIP is a risk factor for VTE. Since the study of Magaz did not include patients with JAK2V617F, whether VTE risk is associated with mutations in specific genes, and whether these patients are exposed to a higher risk of recurrence are important questions that need to be addressed in large multicentric series.

The third feature of interest of the Carrà paper is the high frequency of JAK2V617F considered part of the CHIP-associated mutations. Three of the 7 patients (43%) with CHIP resulted JAK2V617F mutated, together with 3 patients with DNMT3A and one with EZH2 mutation. CHIP-associated mutations occur in many different genes, the most frequent of which are epigenetic regulators (DNMT3A, TET2 and ASXL1) which account for approximately 70% of the mutations, followed by mutations in RNA splicing genes (SF3B1, U2AF1) and signalling like JAK2.

The extraordinary high frequency of JAK2V617F among the CHIP-associated mutations in SVT subjects, opens the question on how to differentiate MPN-specific mutations from those CHIP-associated. A similar question was raised by Steemsa et al. for the CHIP in normal population when
the authors claimed that detection of a myelodysplastic syndrome (MDS)-associated somatic mutation in a cytopenic patient without other evidence of MDS causes diagnostic uncertainty.\textsuperscript{9}

Carrà et al. claimed his subjects lacked a myeloid disorder because bone marrow biopsies were inconsistent with a WHO-defined MPN. However, diagnosing a MPN in someone with SVT is challenging. The authors itself annotated that the patients had an increased bone marrow cellularity, an increased erythroid component, and occasional hyperplasia of megakaryocytes with dysplasia. These data raise the suspicion of an early MPN.

\textbf{We recently described a new sub-type of MPN frequently associated with SVT.}\textsuperscript{10} The disorder is characterized by normal blood cell concentration, no signs of disease activity, with megakaryocyte hyperplasia and dysplasia, we termed \textit{clonal megakaryocyte dysplasia with normal blood values}. Here we emphasize that our dataset contains other MPN currently considered MPN-unclassifiable in the 2016 WHO classification of myeloid disorders. Many of these persons have idiopathic thromboses (often SVT) and a bone marrow histology showing minimal changes of megakaryocytes that deserve to be more precisely and usefully classified.

In their discussion, Carrà et al. claim CHIP is a clue to the pathophysiology in SVT and a new, easily identifiable risk factor for SVT recurrence. I suggest more careful study of bone marrow histology in persons with an SVT, especially of megakaryocytes, is likely to identify new patients with MPN-associated SVT and consistently address them to a differential strategy of cure.
References


